MedCrave
Step into the World of Research

Urology & Nephrology Open Access Journal

Research Article

Open Access

CrossMark

Association of high altitude hypertension with angiotensin converting enzyme (*ACE*) gene insertion/deletion polymorphism

Abstract

The study included *ACE* gene I/D polymorphism and its association between high altitude hypertension. Genetic, biochemical, anthropometric and Physiometeric results were analyzed using statistical software. The results were non-significant for I/D polymorphism.

Objective: *ACE*is the major enzyme of hypertension and with most commonly reviewed I/D polymorphism. High-altitude exposes various physiological and biochemical changes, which contributes a rise in systemic blood pressure of the body. There are very few studies available in North-India, with a core focus on the high altitude hypertension. Therefore, a current study supported an interest to find out the association of high altitude hypertension with *ACE* gene I/D polymorphism.

Methods: to study the significant association with respect to altitude, genetic, biochemical, anthropometric and physio-metric comparison were conducted among 98 individuals where 489nbeing hypertensive patients and other half being normotensive, inclusive of both males and females. The entire results were finally examined and analyzed using statistical software SPSS 16.0 version.

Results: According to study results, mean arterial blood pressure and triglycerides were significantly ($p<0.05$) associated with SBP among both hypertensive and normotensives. Whereas HDL, LDL-HDL ratio, CHO-HDL were significantly associated only among hypertensive, and age, PP, and SpO2 have been significantly ($p<0.05$) associated with SBP among normotensive, a strong predictor for SBP.

Conclusion: The genotypic observations were visibly linked with the disease, however, the results were statistically non-significant (ID/DD vs. II; OR: 0.54, 95% CI: 0.20-1.44, p= 0.217). A further study with considerate knowledge of noteworthy dynamics, mainly, altitude, population size, and ethnicity are recommended.

Keywords: altitude, cholesterol, blood pressure, polymorphism, hypertension

Volume 5 Issue 1 - 2017

Shikha Chandel,[1,2] Badarud Doza,[1,3] Kumar Digvijay[2]

[1]Department of Human Genetics, Guru Nanak Dev University, India

[2]Department of Nephrology and Research, Sir Ganga Ram Hospital, India

[3]Aligarh Muslim university, off campus Murshidabad, India

Correspondence: Kumar Digvijay, Department of Human Genetics, Guru Nanak Dev University, Amritsar, Department of Nephrology and Research, Sir Ganga Ram Hospital, Delhi, India, Email ibrandigu@gmail.com

Received: November 18, 2016 | **Published:** June 23, 2017

Abbreviations: ACE, angiotensin converting enzyme; AT1R, angiotensin ii type 1 receptor; AT2R, angiotensin II type 2 receptor; BMI, body mass index; CHO, total cholesterol; CHO-HDL, total cholesterol-high density lipoproteins ratio; CI, confidence interval; D, deletion; DBP, diastolic blood pressure; HDL, high density lipoproteins; HWE, hardy weinberg equilibrium; I: insertion; I/D, insertion/deletion; LDL, low density lipoproteins; LDL-CHO, low density lipoproteins-total cholesterol ratio; MAP, mean arterial blood pressure; PP, pulse pressure; PR, pulse rate; OR, odds ratio; RAS, renin-angiotensin System; SBP, systolic blood pressure; TG: triglycerides; VLDL, very low density lipoproteins; WC, waist circumference; WHR, waist-to-hip ratio

Introduction

Human essential hypertension accounts for 90% of the hypertensive population, is a complex multifactorial and polygenic disorder[1,2] affecting large groups with a genetic heritability ranging from 15% to 35%.[3-6] The interplay between environmental and genetic factors is a major determinant of the final phenotype in hypertension.[2] Several genes: angiotensinogen gene (*AGT*), angiotensin I-converting enzyme (*ACE*), angiotensin II type 1-receptor (*AT1-R*) and angiotensin II type 2- receptor (*AT2-R*) have been reported an association with hypertension.[7-11] *ACE* is the major enzyme of the renin-angiotensin-aldosterone system (RAAS), functions conversion of angiotensin I to angiotensin II which binds to plasma membrane receptors, producing arteriolar constriction and a rise in systolic and diastolic blood pressure. *ACE* is encoded by a 21 kb gene with 26 exons, located on chromosome 17. A polymorphism of *ACE* gene involves the insertion (I) and deletion (D) of 287 bp *Alu* repeat sequence near the 3' end of the intron. Physiologically it has been reported *ACE* I/D accounts for 50% of the inter-individual variability of plasma *ACE* concentration.[12-14]

High-altitude environments imply stress factors: hypoxia, cold, humidity, solar radiation, cosmic radiation and isolation, causing many physiological and biochemical changes in body, including structural changes in the walls of small pulmonary arteries, predominantly increased masculinization, increased pulmonary vascular resistance and sustained elevation of pulmonary arterial pressure, instigating high altitude pulmonary hypertension (HAPH).[15-18] In humans, large inter-individual differences exist in the magnitude of the pulmonary pressure response to hypoxia,[19-22] with some subjects demonstrating exaggerated increases in pulmonary arterial pressure.[23,24] There are very few studies available in North-India where the high altitude hypertension has been focused. Therefore, the objective of this study was designed, supporting an interest to find out the association of high altitude hypertension with *ACE* gene I/D polymorphism.

Methods

Study protocol

This study was a prospective observation of genetic and biochemical analysis among hypertensive patients and normotensive controls, to analyze the significant association of hypertension in concordance to altitude. The study protocol was approved by the institutional board of committee and experiments were performed in the registered department of Human Genetics, Guru Nanak Dev University, and Amritsar, India.

Sample collection

A total of 98 individual samples, 49 hypertensive and 49 normotensives, both males and females included, were collected from high altitude areas of Himachal Pradesh and low altitude areas of Punjab. The patient samples were collected from clinics and hospitals and control samples were taken via door to door study. The patient and control data was collected on a pre-designed Performa, referring to demographic and clinical features. A 3-5 ml of peripheral blood from each individual was withdrawn with a sterile disposable syringe, after having the informed consent. Blood and plasma samples were stored differently for genetic and biochemical analysis. Also, the body Physiometeric measurements of individuals were noted, as useful annotations during statistical analysis of overall data.

Genetic studies

To study ACE I/D Polymorphism, DNA isolation using phenol-chloroform method was performed using the blood samples of individuals from both hypertensive and normotensive groups. After confirming the quality of DNA (min. 50ng/µl) using Agarose gel electrophoresis (λ200) and NanoDrop1000 techniques, proceeded the next step of PCR reactions, an enzymatic amplification of DNA fragments (95ºC- 5 min. and 30 sec denaturation, 56ºC- 30 sec. annealing, 72ºC- 30 sec. and 5 min. extension, for 30 cycles), using *ACE* I/D gene specific primers (F- 5'-CTG GAG ACC ACT CCC ATC CTT TCT -3', R- 5'-GAT GTG GCC ATC ACA TTC GTC AGA TTT-3'). The amplicons were analyzed for I/D (I at 490bp and D at 190bp) of the 287bp *Alu* repeats in an *ACE* gene on 1.5% agarose gel, stained with Ethidium Bromide, using the 100pb DNA marker to study the genotyping pattern of both the groups (Figure 1).

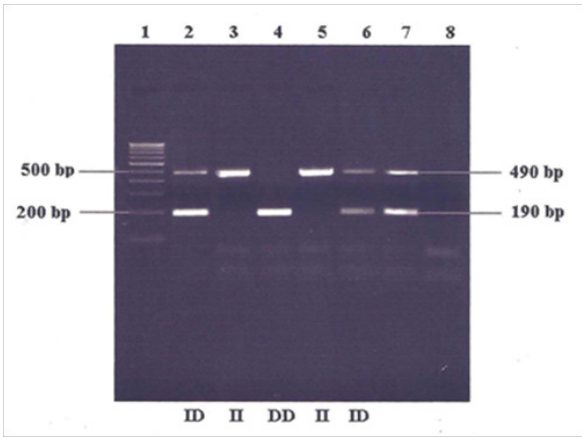

Figure 1 Gel Picture showing I/D polymorphism of ACE gene.
Lane 1: 100 bp DNA ladder
Lane 2-6: Random samples
Lane 7: Positive control
Lane 8: Negative control

Biochemical studies

Total cholesterol (CHO) (desirable <200, borderline 200-239, high >240), triglycerides (desirable <150, borderline 150-199, high 200-500), high density lipopolysaccharides (HDL) (low > 40, high < 50), low-density lipopolysaccharides (LDL) and very low-density lipopolysaccharides (VLDL), HDL-LDL ratios, CHO-LDL ratio were calculated via kit based techniques, using blood plasma separated from the collected blood samples of both groups.

Anthropometric and physiometeric measurements

The height, weight, waist and hip circumference calculated for each individual using standard anthropometric technique and the physio metric variables: systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, taken 2 hours after meal, using the calculated average of 3-4 time measurements via automatic machine, saturated oxygen pressure (SpO2) using pulse oxy-meter, were calculated for both groups.

Statistics

The data collected from genetic, biochemical, anthropometric and Physiometeric studies were analyzed statistically using SPSS (16.0 version), to evaluate the associated significance in this study. All 98 individuals included, were the only eligible candidates supporting WHO (2009) criteria of normal and hypertensive blood pressure measurements in the conducted study. The analysis included, differential statistical comparisons (for Physiometeric, anthropometric and biochemical variables), linear and multivariate regression (to calculate significant predictors of SBP and DBP), risk estimation (odds ratio, CI-95%, for SBP and DBP), allelic frequency distribution (with respect to *ACE* genotypes inclusive of risk factors (odds ratio, CI- 95%), Figure 2), for the individuals of both groups. All statistical tests were two-sided with a significance level of 0.05.

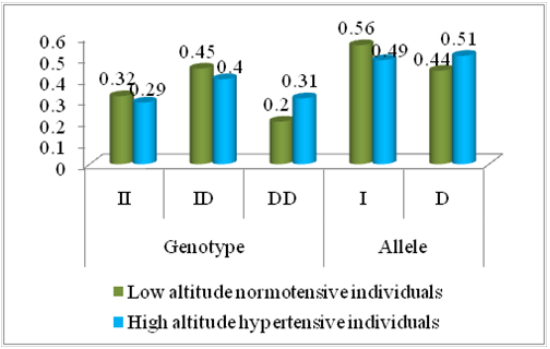

Figure 2 Genotypic and allelic frequencies distributions in high altitude hypertensive individuals and low altitude normotensive individuals.

Results

In this study, we compared descriptive statistics for different anthropometric, psychometric, biochemical and lifestyle variables with a p-value ($p<0.05$) of significance among hypertensive and normotensive individuals (Table 1). The study revealed, mean values of age, SBP, DBP, MAP, PP, SpO2, CHO, LDLs and VLDLs were significantly higher ($p<0.05$) for all the variables, except SpO2, with significant lower p-value among high altitude hypertensive individuals.

Regression models

The descriptive results were further continued by calculating significant predictors of SBP and DBP through univariate regression

analysis. We found during analysis that DBP, MAP, and PP are significantly associated ($p<0.05$) with SBP among both groups whereas height and weight are significantly associated ($p<0.05$) with SBP among normotensive individuals. It was also found during analysis that MAP and triglycerides were significantly associated ($p<0.05$) with SBP among hypertensive and normotensive individuals. HDL, LDL-HDL ratio, and CHO-HDL ratios were significantly associated among hypertensive only and on the other hand age, pulse pressure, and SpO2 were significantly associated ($p<0.05$) with SBP among low altitude normotensive and therefore strong predictor for SBP (Table 2). Table 3 describes, LDL-HDL ratio and CHO-HDL are significantly associated ($p<0.05$) among hypertensive individuals whereas age, mean arterial pressure and pulse pressure were found significantly associated ($p<0.05$) among normotensive individuals with DBP.

Table 1 Descriptive statistics for different studied variables among Hypertensive and Normotensive groups

Variable	Hypertensive			Normotensive			t	p-Value
	N	Mean	SD	N	Mean	SD		
Age(years)	49	55.02	13.52	49	49.87	9.67	2.088	<0.042
Height(cm)	49	1.62	0.085	49	1.64	0.09	0.894	0.376
Weight(kg)	49	71.09	12.26	49	69.56	10.52	0.730	0.469
Body mass index(BMI)(kg/m2)	49	26.96	4.27	49	25.93	3.54	1.375	0.176
Waist circumference(cm)	49	96.44	9.96	49	93.26	10.75	1.568	0.124
Hip circumference(cm)	49	99.43	8.38	49	99.16	7.97	0.166	0.869
Waist-hip ratio	49	0.97	0.06	49	0.94	0.08	1.861	0.69
Systolic blood pressure(mmHg)	49	146.55	17.64	49	130.12	13.22	5.097	<0.000
Diastolic blood pressure(mmHg)	49	90.32	10.06	49	79.97	9.09	5.327	<0.000
MAP(mmHg)	49	109.07	11.57	49	96.69	9.80	5.557	<0.000
Pulse Pressure(mmHg)	49	56.22	12.96	49	50.14	8.84	2.839	<0.007
Pulse rate(counts/min)	49	77.65	14.47	49	78.16	9.83	0.185	0.854
SpO2 (%)	49	97.20	1.92	49	97.91	0.73	2.449	<0.018
Alcohol	49	1.61	0.88	49	1.43	0.67	1.176	0.245
Smoking	49	1.48	0.86	48	1.25	0.56	1.631	0.110
Exercise	49	0.73	0.49	48	0.58	0.57	1.533	0.132
Food habit	49	1.48	0.50	49	1.38	0.49	1.000	0.322
Physical fitness	49	1.89	0.30	49	1.93	0.31	0.629	0.533
Total-cholesterol (CHO)(mg/dl)	41	207.02	88.40	49	153.46	50.39	2.933	<0.006
Triglycerides(mg/dl)	41	199.26	129.38	49	193.59	103.54	0.017	0.987
High density lipoproteins(mg/dl)	41	50.56	28.81	49	45.22	32.45	0.742	0.463
Low density lipoprotein(mg/dl)	41	116.59	94.89	49	69.52	48.64	2.528	<0.016
Very low density lipoprotein	41	39.85	25.87	49	38.71	20.70	3.464	<0.001
LDL-HDL ratio	41	3.00	2.69	49	2.03	1.69	1.616	0.114
CHO-LDL ratio	41	5.01	2.72	49	4.15	2.25	1.192	0.240

HDL, high density lipoprotein, LDL, low density lipoproteins

Table 2 Calculation of significant predictor of systolic blood pressure (SBP) through multivariate regression analysis among high altitude hypertensive and low altitude low altitude normotensive individuals

Variables	High Altitude Hypertensive				Low Altitude Normotensive			
	Coefficient	Std. Error	t	p-Value	Coefficient	Std. Error	t	p-Value
Age(years)	0.370	0.224	1.655	0.105	0.400	0.189	2.12	<0.040
Height(cm)	-1123.1	806.08	1.393	0.170	160.92	105.83	1.52	0.136
Weight(kg)	0.406	0.366	1.107	0.274	-1.13	1.275	0.893	0.377
Body mass index(BMI)(kg/m2)	-0.384	1.258	0.305	0.762	4.498	3.401	1.323	0.193
Waist circumference(WC)(cm)	0.729	0.528	1.380	0.174	-0.364	0.257	1.418	0.163
Hip circumference(cm)	0.001	0.001	1.288	0.204	-0.001	0.005	0.215	1.053
Waist-hip ratio	0.008	0.0198	0.437	0.664	0.045	0.005	0.903	0.371
Mean arterial pressure(mmHg)	3.00	0.02	10.3	<0.001	1.000	0.004	22.43	<0.001
Pulse pressure(mmHg)	1.149	0.117	9.804	1.043	0.667	0.004	13.24	<0.001
Pulse rate(counts/min)	0.117	0.011	1.033	0.307	0.134	0.188	0.711	0.481
SaO2 (%)	0.602	0.859	0.700	0.487	-5.76	2.486	2.321	<0.025
Total cholesterol(CHO)(mg/dl)	0.002	0.030	0.095	0.924	-0.014	0.042	0.340	0.735
Triglycerides(mg/dl)	0.040	0.020	1.984	<0.050	0.033	0.019	1.848	<0.05
HDL(mg/dl)	-0.182	0.092	1.958	<0.050	-0.095	0.063	0.015	0.988
LDL(mg/dl)	0.0405	0.053	0.763	0.450	-0.034	0.060	0.578	0.566
VLDL(mg/dl)	-0.09	0.157	0.595	0.556	0.191	0.141	1.350	0.184
LDL-HDL ratio	-14.08	6.127	2.299	<0.027	1.864	4.428	0.421	0.676
CHO-HDL ratio	12.9	4.978	2.593	<0.014	-0.827	2.942	0.281	0.780

HDL, high-density lipoproteins; LDL, low-density lipoproteins;VLDL, very low-density lipoproteins; R2: percent of variance

Citation: Chandel S, Doza B, Digvijay K. Association of high altitude hypertension with angiotensin converting enzyme (*ACE*) gene insertion/deletion polymorphism. *Urol Nephrol Open Access J.* 2017;5(1):212–217. DOI: 10.15406/unoaj.2017.05.00155

Table 3 Calculation of significant predictor of diastolic blood pressure (DBP) through multivariate regression analysis among hypertensive and normotensive individuals

	High Altitude Hypertensive				Low Altitude Normotensive			
Variables	**Coefficient**	**Std. Error**	**T**	**p-Value**	**Coefficient**	**Std. Error**	**t**	**p-Value**
Age(years)	0.093	0.144	0.647	0.522	0.009	0.004	2.094	<0.042
Height(cm)	39.60	20.95	0.078	0.938	27.18	14.16	1.919	0.062
Weight(kg)	0.017	0.222	0.807	0.424	0.349	0.188	1.853	0.071
Body mass index(BMI)(kg/m2)	0.059	0.812	0.073	0.942	-0.80	0.576	1.399	0.169
Waist circumference(WC)(cm)	3.43	2.218	1.547	0.129	-0.28	1.918	0.148	0.883
Hip circumference(cm)	-3.37	2.009	1.679	0.100	0.459	1.730	0.265	0.792
Waist-hip ratio	-31.4	20.60	1.413	0.165	14.52	18.742	0.076	0.939
Mean arterial pressure(mmHg)	31.6	25.01	1024	0.625	1.00	0.0043	23.89	<0.001
Pulse pressure(mmHg)	0.149	0.117	1.274	0.209	-0.33	0.0051	6.139	<0.001
Pulse rate(counts/min)	0.117	0.113	1.033	0.307	0.002	0.0040	0.707	0.483
SaO2 (%)	0.602	0.859	0.700	0.487	0.002	0.0057	0.452	0.654
Total cholesterol(CHO)(mg/dl)	0.05	0.019	0.306	0.761	-0.04	0.0280	1.580	0.121
Triglycerides(mg/dl)	0.22	0.012	1.758	0.087	0.021	0.0127	1.717	0.093
HDL(mg/dl)	-0.05	0.058	0.897	0.375	-0.042	0.0421	1.018	0.314
LDL(mg/dl)	0.07	0.018	0.391	0.698	-0.025	0.0413	0.618	0.540
VLDL(mg/dl)	0.115	0.069	1.668	0.104	-0.024	0.0982	0.250	0.804
LDL-HDL ratio	-4.00	2.041	1.959	<0.05	-0.913	2.987	0.030	0.761
CHO-HDL ratio	4.422	2.013	2.197	<0.035	1.343	1.985	0.677	0.502

HDL, high-density lipoproteins; LDL, low-density lipoproteins;VLDL, very low-density lipoproteins; R2, percent of variance

*ACE*allele and genotype with different genetic inheritance models between high altitude hypertensive cases and low altitude normotensive controls was shown in Table 4. The genotype and allele distributions of the *ACE* gene are almost similar and did not differ significantly between control and cases. No deviation from HWE has been found within both case and control group separately. However, there was a suggestive evidence of an association in a recessive model (OR: 0.83, 95% CI: 0.33-2.05, p= 0.681). It was also evident from the study that dominant model of inheritance has some protective impact with respect to high altitude hypertension but, the result found were not statistically significant (OR: 0.54, 95% CI: 0.20-1.44, p= 0.217) (Table s1 $ s2).

Table 4 Distribution of frequencies of Angiotensin Converting Enzyme (ACE) genotypes, alleles and genetic models in High Altitude Hypertensive Cases and Low Altitude normotensive Controls. Data are a number of subjects with each genotype and allele (frequency in percentage). OR- Odds Ratio, CI- Confidence Interval. ORs for different modes of inheritance have been calculated

Total N (control + case)=88

	Genotype (%)			Allele (%)		p-Value		Dominant Model (II/DD vs. II)		Co-Dominant Model (DD vs. ID)= (ID vs. II)		Recessive Model (DD vs. II/ ID)		Test for H.W. Equilibrium	
Study	**II**	**ID**	**DD**	**I**	**D**	**Genotype**	**Allele**	**OR (95%CI)**	**p-Value**	**OR (95% CI)**	**p-Value**	**OR (95% CI)**	**p-value**	***x2***	**P**
Control (n=46)	15 (32)	22 (45)	9 (20)	54 (56)	40 (44)	0.46	0.306	0.54 (0.20-1.44)	0.217	0.76 (0.43-1.33)	0.331	0.83 (0.33-2.05)	0.681	0.033	0.855
Case (n=42)	12 (29)	17 (40)	13 (31)	41 (49)	43 (51)									1.516	0.218

Discussion

The study described the association between the *ACE* variant of high altitude hypertension in North Indian population. Many studies have shown a significant *ACE* gene D allele with essential hypertension.[25-31] On the other hand, several researchers have shown no significant differences in the allele and genotype distribution of *ACE* gene polymorphism between low altitude normotensive control and high altitude hypertensive cases.[32-39] The increase in body size has seen to be positively associated with blood pressure. There is a hypothesis that high body weight individuals are more likely to develop systemic hypertension at high altitude. On exposure to high altitude, systemic hypertension results from sympathetic stimulation and it may continue for many weeks. The involvement of the renin-angiotensin-aldosterone system (RAAS) in the control of the salt and water balance and thereby blood pressure is well known during hypoxia and high altitude exposure.[35,36] At high altitude renal secretion is stimulated by decreased renal blood flow,[37] which in turn activates the RAAS.[16]

In the present study, significant differences were observed in hypertension parameters such as pulse pressure, total cholesterol, low-density lipoproteins and very low-density lipoproteins. The mean values of all these parameters have been observed higher in high altitude hypertensive individuals, however, the content of O2 saturation (SpO2) has been higher in low-altitude individuals. In the present study of a small data set, the overall frequencies of the risk allele (D) have been higher in high altitude hypertensive individuals but, not significant (p =0.47) as compared to low altitude normotensive individuals. Therefore, D allele association hypothesis of hypertension in high altitude have not reflected to be true in the present study. The same also is true for I allele. The different covariates of hypertension such as body mass index, waist-hip ratio, waist circumference, hip circumference etc. have also not seen significantly different

between high altitude hypertensive individuals. This observation also strengthens the present genotypic association analysis which did not show any association between *ACE* gene polymorphism in hypertension in high altitude cases.

In some population, the I allele may be in linkage disequilibrium with a mutation elsewhere in the gene, whereas in other population the D allele might be in linkage disequilibrium with the different *ACE* mutation. This might explain the association of essential hypertension and *ACE*-I allele. The recently described variety of potentially functionally variants in the *ACE* gene may support the alternative hypothesis.[38-40] However, studies in North Indian Punjabi[41-45] reported that diseases such as central obesity, type-2 Diabetes Miletus, and hyperlipidemia are more common but they have a low risk of developing cardiovascular diseases due to their strong genetic background. The low frequency of *ACE* DD genotype in this population might provide a protective effect for cardiovascular diseases. However, in this regard, not many data are available to support the present findings of this population.[46]

Conclusion

The present analysis suggests that this ACE gene polymorphism has no major influence on the susceptibility to elevate blood pressure phenotype with respect to high altitude. In the meantime, it should be noted that the present study has been carried out on a small sample size; despite this fact the findings which have been in homogenous population base study cannot be ignored.

Limitations

The study was carried as the thesis work of a Master's student, therefore limited the number of subjects to be enrolled due to the short duration of time. Although the places were chosen were new for the study but the altitude was not really that higher to prove a significant association even in the lesser number of samples. It might have been more convincing with a better knowledge of population statistics and a larger group of cases enrolled. Though the results in conducted study could not give expected statistics but the non-statistical genotypic frequency results observed has given a supportive overview of *ACE* gene association with High altitude hypertension. If the study is conducted further with a larger data groups the results might be as promising as expected.

Acknowledgements

We gratefully acknowledge the study investigators, fellow researchers, clinicians, and patients and individuals who volunteered to participate in the study. The supported funding and work were done in the department of Human Genetics, Guru Nanak Dev University, and Amritsar, India. The work was re-analyzed by S.C and edited by K.D at institute of renal sciences and research, Sir Ganga Ram Hospital. Delhi, India.

Conflicts of Interset

None.

References

1. Nowak MA, Sasaki A, Taylor C, et al. Emergence of cooperation and evolutionary stability in finite populations. *Nature*. 2004;428(6983):646–650.
2. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell*. 2001;104(4):545–556.
3. Agarwal A, Williams GH, Fisher NDL. Genetics of Human Hypertension. *Trends Endocrinol Metab*. 2005;16(3):127–133.
4. Marteau JB, Zaiou M, Siest G, et al. Genetic determination of blood pressure regulation. *J Hypertens*. 2005;23(12):2127–2143.
5. Tanira MO, Al Balushi KA. Genetic variations related to hypertension: a review. *J Hum Hypertens*. 2005;19(7):7–19.
6. Gong M, Hubner N. Molecular genetics of human hypertension. *Clin Sci (Lond)*. 2006;110(3):315–326.
7. Jin JJ, Nakura J, Wu Z, et al. Association of angiotensin II type 2 receptor gene variant with hypertension. *Hypertens Res*. 2003;26(7):547–552.
8. Kikuya M, Sugimoto K, Katsuya T, et al. A/C1166 gene polymorphism of the angiotensin II type 1 receptor (*AT1*) and ambulatory blood pressure: the Ohasama Study. *Hypertens Res.* 2003;26(2):141–145.
9. Ono K, Mannami T, Baba S, et al. Lack of association between angiotensin II type 1 receptor gene polymorphism and hypertension in Japanese. *Hypertens Res*. 2003;26(2):131–134.
10. Yamagishi K, Iso H, Tanigawa T, et al. High sodium intake strengthens the association between angiotensinogen T174M polymorphism and blood pressure levels among lean men and women: a community based study. Hypertens Res. 2004;27(1):53–60.
11. Tamaki S, Nakamura Y, Tabara Y, et al. Combined analysis of polymorphisms in angiotensinogen and adducin genes and their effects on hypertension in Japanese sample: the Shigaraki Study. *Hypertens Res*. 2005;28(8):645–650.
12. Riget B, Hubert C, Alhenc-Gelas F, et al. An insertion–deletion polymorphism in the angiotensin–I–converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest.* 1990;86(4):1343–1346.
13. Morshed M, Khan H, Akhteruzzaman S. Association between Angiotensin I–Converting Enzyme Gene Polymorphism and Hypertension in Selected Individuals of the Bangladeshi Population. *J Biochem Mol Biol*. 2002;35(3):251–254.
14. Zhang L, Miyaki K, Araki J, et al. Interaction of Angiotensin I–Converting Enzyme Insertion–Deletion Polymorphism and Daily Salt Intake Influences Hypertension in Japanese Men. *Hypertens Res.* 2006;29(10):751–758.
15. Malhotra MS, Selvamurthy W, Purkayastha SS, et al. Responses of the autonomic nervous system during acclimatization to high altitude in man. *Aviat Space Environ Med*. 1076;47(10):1076–1079.
16. Kumar R, Pasha MAQ, Khan AP, et al. Association of high–altitude systemic hypertension with the deletion allele–of the angiotensin–converting enzyme (*ACE*) gene. *Int J Biometeorol*. 2003;48(1):10–14.
17. Hislop A, Reid L. New findings in pulmonary arteries of rats with hypoxia–induced pulmonary hypertension. *Br J Exp Pathol*. 1976;57(5):542–554.
18. Meyrick B, Reid L. Hypoxia–induced structural changes in the media and adventitia of the rat hilar pulmonary artery and their regression. *Am J Pathol.* 1980;100(1):151–178.
19. Mirrakhimov M, Winslow R. *The cardiovascular system at high altitude.* In: M Fregle, et al., editors. Environmental physiology Oxford University Press, Oxford. 1986. p. 1241–1258.
20. Wensel R, Opitz CF, Ewert R, et al. Effects of iloprost inhalation exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. *Circulation*. 1999;101(20):2388–2392.
21. Palevsky HI, Fishman AP. Chronic cor pulmonale: etiology and management. *JAMA*. 1990;263(17):2347–2353.
22. Westcott RN, Fowler NO, Scott RC, et al. Anoxia and human pulmonary vascular resistance. *J Clin Invest.* 1950;30(9):457–470.

23. Vogel HJK, Weaver WF, Rose LD, et al. *Pulmonary hypertension on exertion in normal man living at 10,150 feet (Leadville, Colorado)Editor Normal and Abnormal Pulmonary Circulation*, Basel, 1963. p. 289–291.

24. Almaz AA, Sarybaev AS, Sydykov AS, et al. Characterization of high altitude pulmonary hypertension in Kyrgyz:Association with ACE genotype. *Am J Respir Crit Care Med*. 1992;166(10):1396–1402.

25. Morris T, Takeguchi Y, Takeda R. Angiotensin converting enzyme polymorphism and essential hypertension. *Lancet*. 1964;343(8889):125.

26. Chiang FT, Chern TH, Lai ZP, et al. Age–and gender–dependent association of the angiotensin–converting enzyme gene with essential hypertension in a Chinese population. *J Hum Hypertens.* 1966;10(12):823–826.

27. Nakano Y, Oshima T, Hiraga H, et al. genotype of the angiotensin 1 converting enzyme gene is a risk factor for early onset of essential hypertension in Japanese patients. *J Lab Clin Med.* 1998;131(6):502–506.

28. Isbir T, Yilmaz H, Ağaçhan B, et al. Association between angiotensin–converting enzyme gene polymorphism and coronary artery disease. *IUBMB Life*. 1999;48(2):205–207.

29. Higaki J, Baba S, Katsuya T, et al. Deletion allele of angiotensin–converting enzyme gene increases risk of essential hypertension in Japanese men: the Suita Study. *Circulation*. 2000;101(17):2060–2065.

30. Hsich MC, Lin SR, Hsich TJ, et al. Increased frequency of angiotensin converting enzyme DD genotype in patients with type 2 diabetes mellitus. *Nephrology Dialysis Transplant*. 2000;15(7):1008–1013.

31. Mesbabahuddin Azam M, Chowdhury N, Akhteruzzaman S. Angiotensin I–converting enzyme gene polymorphism in type 2 diabetic patients with Nephropathy. *Nephrol Dial Transplant*. 2007;7:14–21.

32. Sivakova D, Lajdova A, Basistova Z, et al. Relationships between blood pressure, polymorphism of angiotensin–converting enzyme (ACE), body composition and biochemical characteristics in elderly Slovaks. *Anthropol Anz*. 2008;66(2):199–209.

33. Dankova Z, Sivakova D, Luptakova L, et al. Association of ACE(I/D) polymorphism with metabolic syndrome and hypertension in two ethnic groups in Slovakia. *Anthropol Anz*. 2009;67(3):305–316.

34. Badaruddoza, Kumar R. Cardiovascular risk factor and familial aggregation of blood pressure with respect to anthropometric variables in a scheduled caste population in Punjab, a North Indian state. *Anthropol Anz*. 2009;67(2):111–119.

35. Sutton JR, Viol GW, Gray GW, et al. Renin, alodsterone, electrolyte and cortisol responses to hypoxic decompression. *J Appl Physiol Respir Environ Exerc Physiol*. 1977;43(3):421–424.

36. Keynes RJ, Smith GW, Slater JDH, et al. Renin and aldosterone at highaltitude in man. *J Endocrinol*. 1982;92(1):131–140.

37. Pauli HG, Truniger B, Larsen JK, et al. Renalfunction during prolonged exposure to hypoxia and carbonmonoxide. I. Glomerular filteration and plasma flow. *Scand J Clin Lab Invest Suppl*. 1968; 22:55.

38. Morrell NW, Saryabae AS, Alikhan A, et al. ACE genotype and risk of high altitude pulmonary hypertension in Kyrghyz highlanders. *Lancet*. 1999;353(9155):814.

39. Zhu X, Bouzekri N, Southam L, et al. Linkage and association analysis of angiotensin I–converting enzyme (ACE)–gene polymorphisms with ACE concentration and blood pressure. *Am J Hum Genet*. 2001;68(5):1139–1148.

40. Dehnert C, Weymann JRN, Montgonery HE, et al. No Association between High–Altitude Tolerance and the *ACE* I/D Gene Polymorphism. *Med Sci Sports Exerc.* 2002;34(12):1928–1933.

41. Badaruddoza, Sawhney R. Familial aggregation of blood pressure with respect to anthropometric variablesin business community of Punjab, a north Indian state. *Coll Antropol*. 2009;33(4):1023–1032.

42. Badaruddoza, Kaur N, Barna B. Inter–relationship of waist–to–hip ratio (WHR), body mass index (BMI) and subcutaneous fat with blood pressure among University going Punjabi Sikh and Hindu females. *International Journal of Medicine and Medical Science*. 2010;2(1):5–11.

43. Kaur T, Bishnoi D, Badaruddoza. Effect of sex on prevalence of type 2 diabetes mellitus (T2DM) with respect to blood pressure, BMI and WHR among Punjabi Population. *International Journal of Medical Science*. 2010;2(9):263–270.

44. Kumar R, Badaruddoz. Familial aggregation and heritability for cardiovascular risk factors: A family based study in Punjab. *Natural Sciences*. 2010;2(7):732–736.

45. Badaruddoza, Kaur P. Famillial patterns of blood pressure with respect to anthropometric variables among Lobana (Nomadic origin) population in Punjab, India. *Asia Pacific Journal of Public Health*. 2010;24:104–116.

46. Badaruddoza, Neha Sudhir. No Evidence for Association between ACE Gene Insertion (I)/Deletion (D) Polymorphism and Hypertension in North Indian Punjabi Population. *International Journal of Human Genetics*. 2012;12(3):179–185.

Citation: Chandel S, Doza B, Digvijay K. Association of high altitude hypertension with angiotensin converting enzyme (*ACE*) gene insertion/deletion polymorphism. *Urol Nephrol Open Access J.* 2017;5(1):212–217. DOI: 10.15406/unoaj.2017.05.00155